Respiratory Physiology & Neurobiology 262 (2019) 49–56

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Protective effect of heart rate variability biofeedback on stress-induced lung function impairment in asthma

Niloofar Taghizadeh[a], Alireza Eslaminejad[b], Mohammad Reza Raoufy[a,*]

[a] Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[b] Chronic Respiratory Diseases Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Asthma
Stress
Airway constriction
Heart rate variability biofeedback

ABSTRACT

Psychological stress can provoke airway constriction in asthmatic patients, which may be because of autonomic nervous system dysfunction in asthma. We investigated the effect of enhancing respiratory sinus arrhythmia using heart rate variability biofeedback (HRV-BF) on spirometry performance and HRV indices during stress induced by Stroop Color-Word interference test in asthmatic patients and healthy volunteers. Stress caused decrease in FEV1%, FVC%, and PEF% compared to baseline in asthmatic patients, but not in healthy subjects. A single short duration episode of HRV-BF not only had a protective effect on stress-induced airway constriction, but also significantly augmented the level of FEV1% and FVC% as compared with their own baseline. Also, there was a significant correlation between HRV changes and the augmentation of spirometry performance in asthmatic patients receiving HRV-BF. Our findings indicated that even a single short duration episode of HRV-BF can decrease susceptibility to stress-induced lung function impairment in patients with asthma, which may be through the modulation of respiratory sinus arrhythmia.

1. Introduction

Asthma is one of the most common chronic disorders in the world, characterized by reversible airway obstruction and heightened airway reactivity (Global Initiative For Asthma (GINA), 2017). Although asthma can be commonly affected by allergens, exercise, and infection, growing numbers of evidence suggest an association between psychological stress and the aggravation of asthma symptoms, more frequent exacerbations, and increased use of emergency and general health services (Lavoie et al., 2005; Martínez-Moragón et al., 2003; Ten Brinke et al., 2001). Psychological stress can provoke airway constriction in asthmatic patients. For instance, experimental stress induction is associated with a reduction in forced expiratory volume in 1 s (FEV1) and respiratory resistance in patients with asthma compared to healthy controls (Janssens et al., 2017; Kullowatz et al., 2008; Rietveld and van Beest, 2007; Ritz et al., 2012). In addition, sustained stress-induced airway constriction may make patients susceptible to experiencing more asthma attacks in their daily lives (Ritz et al., 2012). There is evidence indicating that exacerbation occurs in 20–35% of asthmatic patients during periods of stress (Isenberg et al., 1992) and 10–15% of the asthma exacerbation is caused by psychological stress (Koyanagi et al., 2009).

Chronic stressors lead to the releasing of stress hormones such as catecholamines and cortisol by activating the sympathetic–adrenal–medullary axis (SAM) and hypothalamus-pituitary-adrenal (HPA) axis respectively, which may be related to the subsequent exacerbation in asthma (Kullowatz et al., 2008). Moreover, long-term stress could elevate T-helper2 cells, which may cause airway inflammation and exacerbated asthma (Kullowatz et al., 2008). However, these processes are activated by long-term stress and the underlying mechanism of short-term stress-induced airway constriction is not clear.

There is evidence that an autonomic imbalance in asthma might be an important contributing factor for these exacerbations (Isenberg et al., 1992; Lehrer et al., 2002). It has been suggested that psychological stress influences asthma by altering the activity of the autonomic nervous system (ANS). Pharmacological blockade of airway cholinergic receptors significantly attenuates emotion-induced airway constriction (Ritz et al., 2010). Additionally, increase in high-frequency heart rate variability, which is suggestive of vagal activity, is associated with greater airway resistance measured after the presentation of a distressing film (Miller et al., 2009). Moreover, increased stress activates the HPA axis and the sympathetic nervous system, possibly leading to immune-regulatory changes such as the production of cytokine type 2 (Kullowatz et al., 2008). Organs of the immune system are innervated

* Corresponding author at: Tarbiat Modares University, Nasr Bridge, Jalal Al Ahmad Highway, Tehran, Iran.
E-mail address: raoufy@modares.ac.ir (M.R. Raoufy).

https://doi.org/10.1016/j.resp.2019.01.011
Received 6 November 2018; Received in revised form 10 January 2019; Accepted 25 January 2019
Available online 26 January 2019
1569-9048/

by sympathetic postganglionic neurons that express adrenergic receptor subtypes. Norepinephrine regulates immune cell activity through these adrenergic receptors (Kullowatz et al., 2008). It appears that stress-induced airway constriction has been observed to be more pronounced in patients with asthma compared to healthy subjects (Ritz et al., 2012), because of ANS dysfunction in asthma (Garcia-Araújo et al., 2015; Garrard et al., 1992; Souza et al., 2010). Therefore, improving ANS activity may be a protective strategy against stress-induced asthma attack.

Heart rate variability biofeedback (HRV-BF) is a behavioral method that causes subjects to breath approximately 6 times per minute (~0.1 Hz) in order to maximize respiratory sinus arrhythmia (RSA), which reflects vagus nerve function (Lehrer et al., 2013, 2003; Vaschillo et al., 2006, 2002). This approach has been used to modulate vagal and sympathetic modulation in a variety of clinical disorders, such as anxiety and hypertension (Lehrer et al., 2003). There are reports indicating that HRV-BF has clinically significant effects on pulmonary function and asthma symptoms. Asthmatic patients receiving long-term HRV-BF as a complementary treatment have displayed improved spirometry performance and respiratory resistance, as well as a decrease in the frequency of exacerbations, while receiving a lower dose of asthma medications (Lehrer et al., 2004, 2018; Lehrer et al., 2000a,b). However, no study has investigated the effect of HRV-BF on emotion-induced airway constriction in asthma so far.

Taken together, since autonomic imbalance is considered as an important contributing factor in airway constriction during psychological stress and that previous reports have demonstrated that even a single short duration episode of HRV-BF (Prinsloo et al., 2013) can improve autonomic reactivity, we hypothesized that HRV-BF may modulate RSA and decrease susceptibility to stress-induced lung function impairment in patients with asthma. To examine this hypothesis, we aimed to investigate the effect of a single HRV-BF on HRV indices during stress induction using the Stroop Color-Word interference test, and on spirometry performance in the immediate post-stress period in asthmatic patients and healthy volunteers.

2. Methods

2.1. Participants

Forty four age-matched women, including 22 healthy volunteers and 22 asthmatic patients, 20–35 years of age with disease duration of 8–15 years, referred to the outpatient clinic of Masih Daneshvari Lung Hospital (Tehran, Iran), were enrolled in this study. Asthma was diagnosed by pulmonologists based on clinical symptoms and pulmonary function. All patients in this study had atopic mild asthma as indicated by an FEV1 between 60 and 85% of predicted values (National Asthma Education and Prevention Program, 2007). Also, controlled asthma was defined based on the National Asthma Education and Prevention Program (NAEPP) guidelines (National Asthma Education and Prevention Program, 2007). Atopy was assessed by skin prick testing methods. All patients received beta agonist and corticosteroid medications. They were medication-free for at least 48 h before the examinations.

Patients with history of smoking, anxiety related disorders, chronic medical problems (neurological impairment, cardiovascular disease etc.), or medications affecting the respiratory or autonomic nervous systems within the past month, as well as overweight (BMI $\geq 25\,kg/m^2$) or underweight (BMI $< 18.5\,kg/m^2$) subjects (WHO Expert Consultation, 2004) were excluded.

The day of menstrual cycle was assessed based on the onset of the last menstrual period. The study was approved by the ethics committee of Tarbiat Modares University. All participants signed informed written consent prior to participation in the study.

The participants were randomly allocated to an HRV-BF (asthma/HRV-BF, healthy/HRV-BF) or a control group (asthma/control, healthy/control). Each group consisted of 11 subjects.

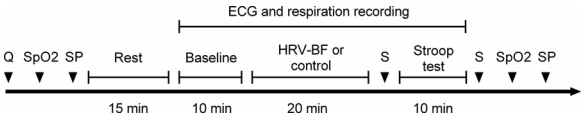

Fig. 1. The time line of the protocol during the experimental procedures.
The main psychophysiological procedures consisted of events as the following: baseline and post-Stroop test spirometry assessment, ECG and respiration recording, HRV-BF procedures, Stroop test, pre- and post-Stroop test stress assessment. SpO2 and pulse rate were continuously monitored throughout experimental procedures.
Q: questionnaires; SpO2: oxygen saturation; SP: spirometry; S: stress scale; HRV-BF: heart rate variability biofeedback

2.2. Experimental procedures

The main psychophysiological procedures that were taken in this study consisted of the following (Fig. 1):

Baseline and post-Stroop test spirometry assessment: Lung function was measured using a spirometer (Pony Spirometer, Cosmed, Italy). Spirometry was performed according to the American Thoracic Society (ATS) criteria. We used FEV1, FVC (forced vital capacity), FEV1/FVC, and PEF (peak expiratory flow) with predicted values adjusted for age, sex, height and race.

ECG and respiration recording: ECG and respiration was recorded during baseline (5 min in a quiet sitting and eyes opened condition), throughout the HRV-BF/control (20 min), and Stroop test (10 min). ECG data was collected from electrodes on the right arm and left leg (Lead II) that were band-pass filtered between 0.5 and 35 Hz and digitized at a 1 KHz sampling rate (Powerlab, ADInstruments, Australia). Respiration signal was recorded at a 1 KHz sampling rate with a low-pass filter of 10 Hz from a pneumotrace band (AD-Instruments, Australia) fastened at the level of umbilicus (Raoufy et al., 2013). Heart rate (HR) and respiratory rate (RR) were real-time calculated and displayed simultaneously with ECG and respiration signals on commercially available software (ChartPro 7, ADInstruments, Australia) (Raoufy et al., 2016; Shirazi et al., 2013).

HRV-BF procedures: a “pacing stimulus” was provided to generate the maximum amplitude of HRV for each individual. For this purpose, a ball was moved up and down on the computer screen at the target respiratory rate (approximately 6 times per minute). Participants were trained to breathe abdominally at the rate of that stimulus. During 20 min of HRV-BF, the beat-to-beat cardiotachometer display was superimposed on respiration signal and participants were taught to breathe approximately in phase with heart rate alterations to maximize RSA (Lehrer et al., 2000a,b). Control subjects were instructed to maintain a state of relaxed alertness and an appropriate selection of classical music, according to individual preferences, was used to induce relaxation (Lehrer et al., 2004).

Stroop test: The Stroop color-word task has been commonly used as a laboratory stress tool for studying human psychophysiological response to stress (Bali and Jaggi, 2015). This test induces subjective stress with concomitant increasing of autonomic reactivity (Delaney and Brodie, 2000). The original Stroop color-word task evaluates the ability of a person to inhibit automatic verbal responses (Stroop, 1935). In this study, we asked subjects to respond by pressing keyboard buttons instead of responding verbally. The different word denotes the names of some colors displayed in an unlike manner (e.g., the word “blue” is written in “red” instead of “blue”). Participants were asked to quickly respond by pressing one of four buttons to specify the color of the word. The total time period of the Stroop color-word test was 10 min.

pre- and post-Stroop test stress assessment: the stress level of subjects was measured using a visual analogue scale from 0 to 10 with labels showing 0 to equal "not at all stress," 5 to equal "moderately stress," and 10 to equal "the worst I've ever felt" (Gift, 1989; Sneed et al., 2001). Subjects were taught to put an X on the scale to reveal how much stress

they were feeling at that moment.

SpO2 and pulse rate were continuously monitored throughout the experimental procedures using pulse oximetry.

2.3. HRV analysis

Our analysis included the ECG signal obtained within a 5-min baseline period, the first 5 min of Stroop test and the last 5 min of Stroop test. Also, for HRV analysis, HRV-BF or control recordings were divided into 4 periods, each lasting 5 min (supplementary data). RR intervals were measured and visually inspected in order to remove artifacts using ChartPro 7 software (ADInstrument, Australia). Subsequently, HRV analysis was performed using Kubios HRV software (MATLAB, version 2.1, Kuopio, Finland).

2.3.1. Linear time domain indices

mean HR and standard deviation of all normal-to-normal intervals (SDNN).

2.3.2. Frequency domain indices

prior to spectrum analysis, RR intervals were converted to equally sampled series using cubic spline interpolation (interpolation rate = 4 Hz). Afterwards, Welch's periodogram (window length = 256 s and overlapping = 50%) was used to calculate low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz) domain of HRV (Malik et al., 1996).

2.3.3. Non-linear indices

the Poincaré plot is a scattergram of correlation between consecutive RR intervals. Short-term (SD1) and long-term (SD2) variability of the Poincaré plot respectively represent RSA and total variability of heart dynamics (Lewis et al., 2006). Sample entropy (SampEn) reflects irregularity of HRV (Richman and Moorman, 2000). Different values of the parameters (m, r, N) are used for entropy analysis of RR-interval series, where N is the length of the time-series, r is the tolerance for accepting matches, and m (embedding dimension) is the length of sequences to be compared. In our analysis, the values for these parameters were m = 2 and r = 0.2 SD.

2.4. Statistical analysis

We used GraphPad Prism V7 (GraphPad Software, San Diego, CA) for statistical analysis of data. Kolmogorov-Smirnov test was used to assess data normality. The significance of differences in baseline characteristics among groups was assessed by a Kruskal–Wallis test for stress level and a one-way ANOVA with a Bonferroni post hoc test for all other parameters. The effects of HRV-BF on spirometry performance and HRV indices during stress in asthmatic patients and healthy controls were analyzed using repeated measures three-way ANOVA, with the Bonferroni post hoc test. A one sample *t*-test was used for determining the percent change of HRV indices from the baseline. Pearson or Spearman correlation coefficients were applied based on the distribution of the data. All results have been presented as mean ± standard error of the mean (SEM) or median (25%–75% percentile). P-values less than 0.05 were considered statistically significant. We also calculated effect size using Cohen's d method.

3. Results

3.1. Baseline characteristics

General characteristics, baseline spirometry parameters, and HRV indices in healthy and asthmatic subjects have been depicted in Table 1. There were no significant differences in age, BMI, menstrual cycle, stress level, SpO2, and respiratory rate among groups. Evaluation of the lung function revealed that asthmatic patients exhibit significantly lower FEV1% ($p = 0.045$), FEV1/FVC% ($p = 0.002$), and PEF% ($p = 0.005$) compared to healthy subjects. Group comparison of HRV showed higher values of HR ($p < 0.001$), lower value of LF ($p = 0.025$), HF ($p = 0.002$), SD1 ($p < 0.001$), SD2 ($p < 0.001$) and SampEn ($p < 0.001$) in patients with asthma, as compared with healthy volunteers.

3.2. Effect of HRV-BF on stress level

As presented in Fig. 2, stress level of subjects after HRV-BF (before Stroop test) was similar to that of controls that were in a state of relaxed alertness. Stroop test significantly increased stress level in all groups ($F = 125.2$, $p < 0.001$). The level of stress induced by Stroop test in healthy subjects was significantly affected by HRV-BF and it was lower in the healthy group receiving HRV-BF than in healthy controls ($p = 0.034$). In asthmatic patients, however, HRV-BF did not have a protective effect on increased stress from Stroop test.

3.3. Effect of HRV-BF on stress-induced alteration of spirometry parameters

Stress and HRV-BF had no significant effect on spirometry parameters in healthy participants (Fig. 3). In the asthmatic control group, the level of FEV1% ($p < 0.001$, $d = 0.63$), FVC% ($p = 0.002$, $d = 0.92$), and PEF% ($p = 0.045$, $d = 0.54$) were significantly reduced during the immediate post-stress period. In asthmatics, HRV-BF not only had a protective effect on decreased spirometry parameters resulting from stress, but also significantly enhanced the level of FEV1% ($p = 0.003$, $d = 0.5$) and FVC% ($p < 0.001$, $d = 0.61$) as compared with their own baseline. However, we found no significant interaction for "healthy/asthma × pre-Stroop test/post-Stroop test" in each spirometry parameters.

3.4. Effect of HRV-BF on stress-induced alteration of HRV indices

SDNN and SD1 of RR intervals, but not heart rate, were significantly increased during HRV-BF, while HRV was not affected by music (supplementary data). Fig. 4 demonstrates percent change in HRV indices from baseline during the first 5 min and the last 5 min of Stroop test. HR significantly increased during stress in both healthy and asthmatic controls ($p < 0.05$). HRV-BF affected HR in patients with asthma in a manner that HR was significantly lower than baseline ($p = 0.038$) and control group ($p < 0.001$) during the first 5 min of stress. SDNN was not affected by stress or HRV-BF in all groups.

3.4.1. SampEn analysis

Stress significantly decreased SampEn of RR-intervals in the asthmatic control group ($p = 0.041$). HRV-BF significantly increased SampEn compared to baseline during the first 5 min of stress in both healthy and asthmatic groups receiving HRV-BF ($p < 0.01$ and $p < 0.001$, respectively) and control group ($p < 0.001$ and $p < 0.001$, respectively). Also, we found significant interaction for "first/second 5 min of stress × healthy/asthma" ($F = 4.78$, $p = 0.032$), "first/second 5 min of stress × HRV-BF/control" ($F = 35.11$, $p < 0.001$), and "first/second 5 min of stress × HRV-BF/control × healthy/asthma" ($F = 4.875$, $p = 0.03$) in SampEn of RR-intervals.

3.4.2. SD1 and SD2

SD1, SD2, and SD1/SD2 of RR-intervals were significantly reduced during stress in the asthmatic control group ($p < 0.05$). These indices were affected by HRV-BF and were significantly increased during the first 5 min of stress among groups receiving HRV-BF compared to baseline ($p < 0.001$) and control group ($p < 0.001$). Also, we found significant interaction for "first/second 5 min of stress × healthy/asthma" ($F = 18.68$, $p < 0.001$), "first/second 5 min of stress × HRV-BF/control" ($F = 22.75$, $p < 0.001$), and "HRV-BF/control × healthy/asthma" ($F = 84.27$, $p < 0.001$) in SD1, for "first/second 5 min of

Table 1
Baseline characteristics of the study subjects.

	Healthy/Control	Healthy/HRV-BF	Asthma/Control	Asthma/HRV-BF	p value
Age (year)	26.3 (0.8)	26.5 (0.9)	28.4 (0.8)	28.5 (0.7)	0.890
Body mass index (Kg/m^2)	22.8 (1.2)	22.6 (0.7)	24.6 (0.9)	23.3 (0.9)	0.403
Menstrual cycle (day)	16.2 (2.1)	15.1 (1.6)	12.5 (1.9)	12.6 (2.1)	0.447
Stress level	1 (1-2)	1 (1-1)	1 (1-2)	1 (1-3)	0.637
O2 saturation (%)	96.5 (0.3)	96.6 (0.3)	96.3 (0.6)	96.7 (0.4)	0.904
Respiratory rate (breaths/min)	11.2 (0.2)	11.3 (0.4)	11.4 (0.2)	11.4 (0.3)	0.935
Spirometry performance					
FEV1 (%)	92.1 (3.2)	90.9 (3.5)	83.8 (3.5) *	80.1 (4.1) *	0.045
FVC (%)	84.5 (3.5)	84.1 (3.9)	88.2 (1.8)	82.4 (3.7)	0.655
FEV1/FVC (%)	109.5 (2.1)	108.6 (2.2)	95.4 (4.5) *	97.3 (2.8) *	0.002
PEF (%)	96.1 (5.0)	97.9 (4.7)	80.1 (3.6) *	74.6 (6.6) *	0.005
HRV indices					
Heart rate (beats/min)	78.1 (1.8)	81.9 (3.2)	88.3 (1.7) *	89.0 (3.0) *	< 0.001
SDNN	45.2 (3.8)	47.1 (5.4)	35.7 (3.3)	41.0 (4.9)	0.292
LF (n.u.)	158.8 (9.6)	162.5 (13.4)	124.8 (4.0) *	138.2 (8.6) *	0.025
HF (n.u.)	520.5 (13.4)	532.9 (27.7)	447.8 (12.4) *	458.8 (9.8) *	0.002
LF/HF	0.31 (0.02)	0.31 (0.03)	0.28 (0.01)	0.3 (0.02)	0.738
SD1 (ms)	28.2 (1.6)	27.0 (1.4)	18.3 (1.0) *	18.1 (0.9) *	< 0.001
SD2 (ms)	43.6 (1.2)	37.7 (1.1)	28.3 (0.7) *	29.7 (1.6) *	< 0.001
SD1/SD2	0.66 (0.05)	0.71 (0.02)	0.65 (0.03)	0.63 (0.05)	0.459
Sample entropy	1.6 (0.04)	1.5 (0.08)	1.0 (0.04) *	1.0 (0.03) *	< 0.001

Data are reported as median (25–75 percentile) for stress level and mean (SEM) for all other variables. HRV-BF: hear rate variability biofeedback; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s. PEF: peak expiratory flow; HRV: heart rate variability; SDNN: standard deviation of all normal-to-normal intervals; HF: high frequency; LF: low frequency; SD1: short-term variability of heart rate; SD2: long-term variability of heart rate. The significance of differences between groups was assessed by a Kruskal–Wallis test for stress level and a one-way ANOVA with a Bonferroni post hoc test for all other variables. Each group consisted of 11 subjects.

* $p < 0.05$ compared to healthy volunteers.

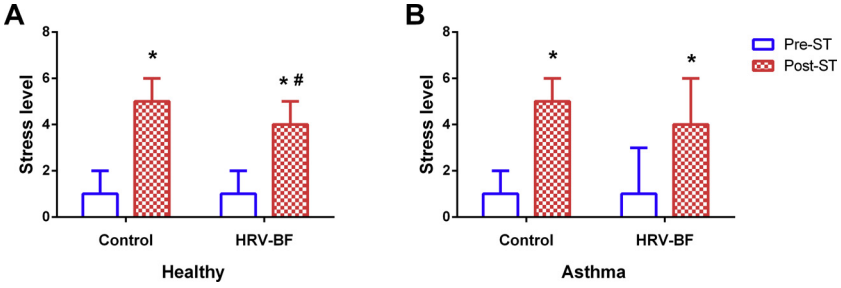

Fig. 2. Effect of heart rate variability biofeedback (HRV-BF) on stress induced by Stroop test in healthy (A) and asthmatic (B) subjects.
Stroop test significantly increased the stress level in the all groups. The level of stress induced by Stroop test was significantly affected by HRV-BF in healthy subjects, but not in the asthmatics.
ST: Stroop test
*: $p < 0.05$ compared to Pre-ST; #: $p < 0.05$ compared to Control

stress × healthy/asthma" ($F = 9.16$, $p = 0.003$), and "HRV-BF/control × healthy/asthma" ($F = 47.54$, $p < 0.001$) in SD2, and for "first/second 5 min of stress × healthy/asthma" ($F = 8.62$, $p = 0.004$) and "HRV-BF/control × healthy/asthma" ($F = 14.54$, $p < 0.001$) in SD1/SD2 of RR-intervals.

3.4.3. LF and HF

stress significantly decreased LF, HF, and LF/HF of RR-intervals in the asthmatic control group ($p < 0.001$). HRV-BF significantly enhanced these indices during the first 5 min of stress in groups receiving HRV-BF compared to their own baseline ($p < 0.001$) and control group ($p < 0.001$). Also, there was significant interaction for "first/second 5 min of stress × healthy/asthma" ($F = 20.45$, $p < 0.001$), "first/second 5 min of stress × HRV-BF/control" ($F = 100.7$, $p < 0.001$), and "HRV-BF/control × healthy/asthma" ($F = 76.66$, $p < 0.001$) in LF, for "HRV-BF/control × healthy/asthma" ($F = 17.46$, $p < 0.001$) in HF, and for "first/second 5 min of stress × healthy/asthma" ($F = 12.56$, $p < 0.001$), "first/second 5 min of stress × HRV-BF/control" ($F = 84.28$, $p < 0.001$), and "HRV-BF/control × healthy/asthma" ($F = 44.45$, $p < 0.001$) in LF/HF of RR-intervals.

3.5. Correlation of spirometry parameters with stress level and HRV indices

There was a significant negative correlation between the percent change of FEV1 and that of stress level ($r = -0.81$, $p = 0.003$) and SD1 ($r = -0.63$, $p = 0.037$) in the asthmatic group receiving HRV-BF. The percent change of FEV1 and FEV1/FVC were significantly correlated with the percent change of HR ($r = -0.64$, $p = 0.037$ and $r = -0.74$, $p = 0.013$, respectively), SD2 ($r = 0.83$, $p = 0.002$ and $r = 0.91$, $p < 0.001$, respectively) and SD1/SD2 ($r = -0.63$, $p = 0.039$ and $r = -0.65$, $p = 0.029$, respectively) in these patients.

4. Discussion

In the present study, stress induced by Stroop test decreased FEV1%, FVC%, and PEF% compared to baseline in asthmatic patients, but not in healthy subjects. A single short duration episode of HRV-BF not only had a protective effect on stress-induced alteration of lung function, but also significantly augmented the level of FEV1% and FVC% as compared with baseline. Moreover, patients with asthma showed deterioration in the HRV indices during the baseline period. Stress significantly affected HRV indices in both healthy and asthmatic control groups. However, stress-induced HRV alteration was larger in asthmatics than in healthy subjects, suggesting an exaggerated response to stress stimulus in asthma. A single short duration episode of HRV-BF modulated heart dynamics revealed by significantly improved HRV indices in patients with asthma, particularly during the first 5 min of stress. Interestingly, there was a significant correlation between improving lung function (FEV1% and FEV1/FVC%) and the alteration of some HRV indices (SD2 and SD1/SD2). This indicates that HRV-BF,

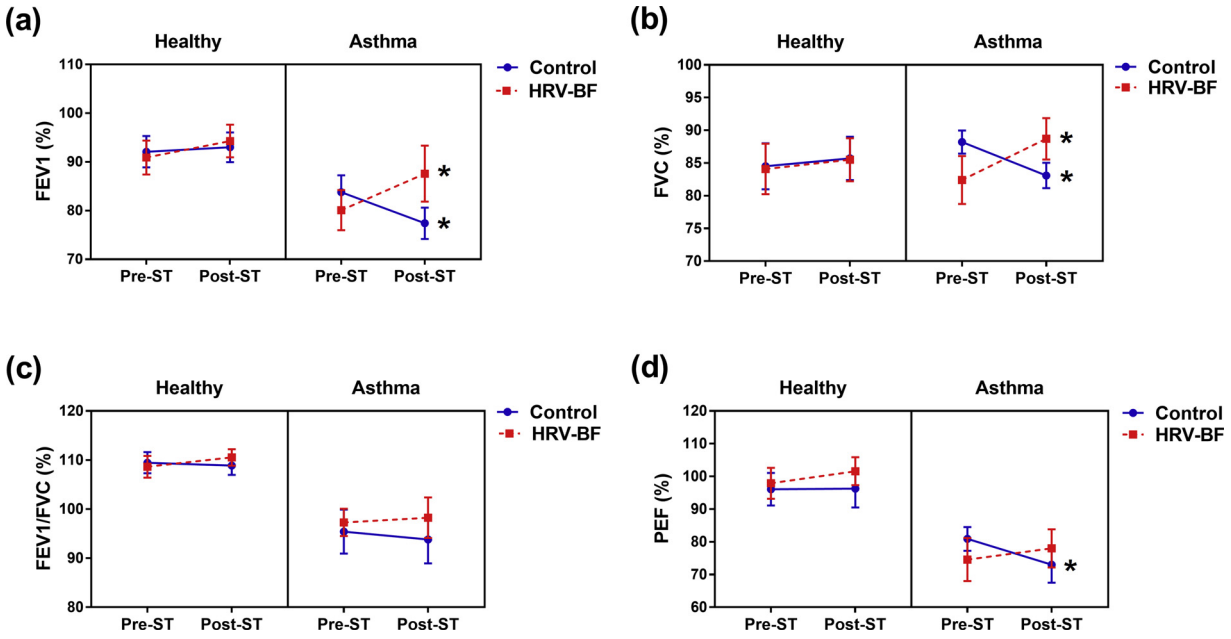

Fig. 3. Effect of heart rate variability biofeedback (HRV-BF) on stress-induced alteration of FEV1% (a), FVC% (b), FEV1/FVC% (c) and PEF% (d).
Stress significantly reduced the level of FEV1%, FVC% and PEF% in patients with asthma, but not in healthy subjects. HRV-BF not only had a protective effect on decreased spirometry parameters due to stress in the asthmatics, but also significantly enhanced the level of FEV1% FVC% as compared with the baseline.
ST: Stroop test; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow
*: $p < 0.05$ compared to Pre-ST

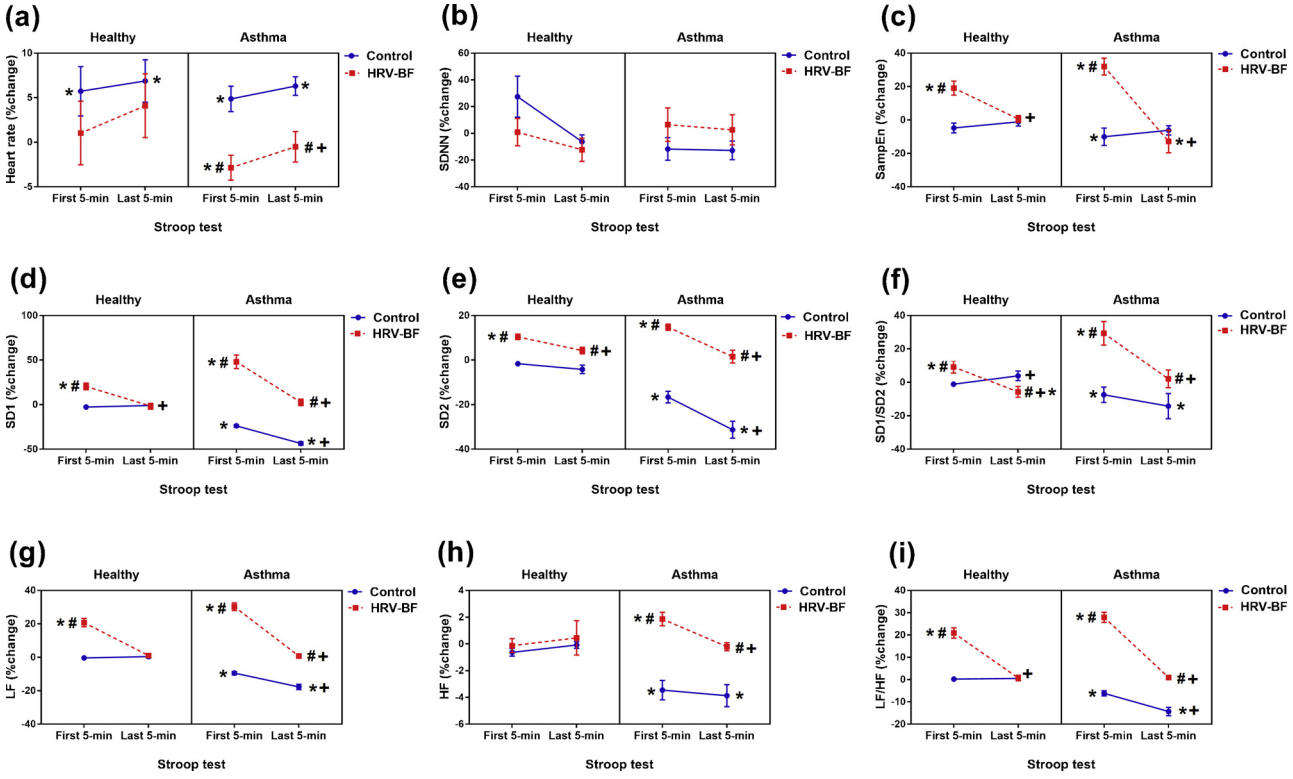

Fig. 4. Effect of heart rate variability biofeedback (HRV-BF) on stress-induced alteration of HRV indices.
(A, B): linear time domain indices, (C–F): non-linear indices, (g–i): frequency domain indices. Stress significantly affected the HRV indices in the both healthy and asthmatic control groups. HRV-BF could modulate heart dynamics, so that the HRV indices were significantly improved particularly during the first 5 min of stress in patients with asthma.
%change is calculated as [(value of each variable - value of baseline) / baseline] ×100
HR: heart rate; SDNN: normal-to-normal intervals; LF: low frequency; HF: high frequency; SampEn: sample entropy
*: $p < 0.05$ compared to baseline (zero value); #: $p < 0.05$ compared to Control; +: $p < 0.05$ compared to First 5-min

even if applied for a single short duration episode, can decrease susceptibility to stress-induced lung function impairment in patients with asthma, possibly through modulating the RSA. Although the effect of HRV-BF on pulmonary function and asthma symptoms has been previously shown in the clinic (Lehrer et al., 2004, 2018; Lehrer et al., 2000a), to the best of our knowledge, this is the first study demonstrating the protective effect of HRV-BF on stress-induced lung function alteration in asthma.

In the asthmatic control group, decreases in spirometry parameters including FEV1%, FVC%, and PEF% were observed after stress as compared with the baseline. This result is in accordance with previous studies that reported an association between the induction of experimental stress and reduced FEV1, as well as increased respiratory resistance in patients with asthma (Janssens et al., 2017; Kullowatz et al., 2008; Rietveld and van Beest, 2007; Ritz et al., 2012). However, it is uncertain whether Stroop test or HRV-BF can affect FEV1 and FVC without changing the FEV1/FVC ratio. Stress can be considered as a stimulus that temporally enhances the severity of obstructive disease such as asthma. FEV1 is an acceptable measurement for evaluating the severity of obstructive disease. However, the FEV_1/FVC ratio is not used for this purpose because, as the disease progresses, long exhalations become difficult for patients, and measurement of FVC becomes less reliable, thus making the ratio less accurate (Qaseem et al., 2011; Rennard et al., 2013). In this line, we found that stress level is negatively correlated with FEV1, but not with FVC or FEV1/FVC. On the other hand, decreased FEV1 and FVC without FEV1/FVC alteration reveal a restrictive manner that is induced by stress in the obstructive context of asthma. However, static lung volume measurements using body plethysmography are needed in order to confirm this concept.

It also supports the suggested hypotheses on the involvement of psychological stress in triggering asthmatic bronchoconstriction. We also found a negative significant correlation between percent change of FEV1 and that of stress level in patients, but not in healthy subjects. Specifically, decline in lung function was not observed in healthy individuals after stress induction, highlighting the particular role of psychological stress in asthmatic complaints. Contrary to our findings, Janssens et al. did not observe any significant difference in respiratory resistance between asthmatic patients and healthy participants during emotional film presentation (Janssens et al., 2017). This discrepancy may result, at least in part, from difference in techniques used for the measurement of lung function and the experimental stress task as well. They assessed respiratory resistance using impulse oscillometry while showing an emotional film, while we measured spirometry performance after the Stroop test. There is evidence that emotionally-induced enhances in respiratory resistance are reversed within 1–2 min (Ritz et al., 2000), and this post-stimulus reduction in resistance is greater in healthy participants than in asthmatics (Janssens et al., 2017). Moreover, in spirometry assessment, deep inspirations and forced expiratory maneuvers affect the airway tone (Gayrard et al., 1979) and may reverse any weak and short-term bronchoconstriction due to stress in healthy volunteers. However, these results propose a specific respiratory response of asthmatics to the onset or offset of psychological stimuli (Janssens et al., 2017; Raoufy et al., 2017).

It has been suggested that psychological stress may affect airway reactivity through autonomic modulation in patients with asthma (Isenberg et al., 1992; Lehrer et al., 2000a, b). On the other hand, there is evidence that asthma is associated with autonomic dysfunction and reduced HRV (Garcia-Araújo et al., 2015; Garrard et al., 1992; Souza et al., 2010). Likewise, we found that patients with asthma present increased HR and decreased HRV as compared with healthy participants during baseline period. Our results are in line with the findings of a previous study which reported an increase in HR in a stable clinic condition in patients with asthma (Garcia-Araújo et al., 2015). On the contrary, Garrard et al. observed a resting bradycardia in asthmatics (Garrard et al., 1992). In addition to HR, there are also controversial results regarding resting HRV indices in asthma. For instance, in agreement with Garrard et al. (Garrard et al., 1992) and in contrast to Garcia-Arau´jo et al. (Garcia-Araújo et al., 2015), we found lower values of LF in asthmatics than in healthy subjects. Also, our findings agreed with Garcia-Arau´jo's study, which had reported a decrease in HF at rest (Garcia-Araújo et al., 2015). In contrast, Souza et al. observed higher HF values in patients with asthma as compared with healthy subjects (Souza et al., 2010). Some of these inconsistencies might be due to differences in anti-asthma treatments and the direct effect of medication on HRV indices. For instance, in a study by Lutfi, although significant differences in HRV indices were detected between asthmatics and healthy participants, these differences disappeared following adjustment for anti-asthma treatment (Lutfi, 2015). In addition, although HF and LF are classically understood as a proxy for the parasympathetic and/or sympathetic nervous system modulations, changes in HRV cannot be interpreted solely by alteration in autonomic activity. For instance, HRV indices alter under inflammatory conditions. There is evidence that inflammatory cytokines correlate negatively with different HRV indices such as HF and LF (Ernst, 2017). Therefore, decreased values of LF and HF can be explained by increase of inflammatory parameters in patients with asthma. However, it seems that future investigations are required in order to verify the results of impaired HRV indices in asthma.

However, abnormality in autonomic function plays an important role in airway impairment in response to stimuli (Canning and Fischer, 2001). An autonomic imbalance can be considered a possible underlying mechanism of exaggerated airway responses to psychological stress in asthma (Isenberg et al., 1992; Lehrer et al., 2002). In this context, our findings revealed a larger stress-induced HRV alteration in asthmatics compared to healthy volunteers. The hyper-reactivity of airways to stress stimuli can justify the significant stress-induced PEF alteration that was observed in patients with asthma, but not in healthy subjects.

In the present study, a single short duration episode of HRV-BF increased HRV indices during stress in both healthy and asthmatics groups. The significant interaction for "healthy/asthma × HRV-BF/control" in HRV indices indicates that the modulatory effect of HRV-BF on heart dynamics, as well as RSA, in asthmatics is larger than that of healthy individuals, despite the higher post-stress alteration of HRV in patients compared to healthy participants. Although stress significantly reduced lung function in the immediate post-stress period, HRV-BF had a protective effect on PEF alteration and, interestingly, enhanced the level of FEV1% and FVC% relative to the baseline. We also found a significant correlation between HRV changes and augmented spirometry performance in asthmatic patients receiving HRV-BF.

Stress significantly reduced LF, HF and LF/HF ratio in patients with asthma, but not in healthy subjects. HRV-BF significantly improved these HRV indices particularly during the first 5 min of stress. HF presents the inflection of respiratory cycle on heart rate and creates functional synchrony between the heart and lungs in order to increase the rate of gas exchange (Censi et al., 2002). It is modulated by the vagus nerve and is to a certain grade similar to RSA, but HF does not measure the vagus tone per se. High LF reflects often enhanced sympathetic activity, but the value of LF is also determined by baroreflex and hence may reflect parasympathetic tone (Goldstein et al., 2011). HRV-BF maximizes RSA and increases baroreflex gain (Lehrer et al., 2013), and thereby can enhance HF and LF values and modulate sympatho-vagal dynamic balance. Therefore, it appears that HRV-BF may affect lung function through autonomic modulation in patients with asthma.

Furthermore, previous investigations have reported that the use of HRV-BF resulted in decreased stress and increased relaxation both during and after the intervention (Mikosch et al., 2010; Prinsloo et al., 2013). In this regard, our results showed that the level of stress induced by Stroop test was lower in the healthy group receiving HRV-BF than in healthy controls. However, HRV-BF could not significantly affect the stress level in asthmatic patients, suggesting that the beneficial effects

of HRV-BF on asthma may not be explained by reduced stress. More investigation is needed in order to understand why the use of HRV-BF does not influence the level of stress induced by Stroop test in asthma. Nevertheless, a significant negative correlation between the percent change of FEV1 and that of stress level was observed in the asthmatic group receiving HRV-BF.

There are a few studies that have investigated the effectiveness of long-term HRV-BF as a complementary treatment for asthma. Preliminary studies have described that HRV-BF increases FEV1 and FEF50 (Lehrer et al., 2000a,b) and decreases respiratory resistance in asthmatic patients (Lehrer et al., 1997). Lehrer et al. have reported that 10 weeks of training in HRV-BF produces decreased respiratory resistance and asthma symptoms (Lehrer et al., 2004). They have also observed that age does not affect the usefulness of the HRV-BF for treating asthma (Lehrer et al., 2006). A recent study indicated that although HRV-BF has some beneficial effects on asthma, it should be considered as a complementary, but not alternative, treatment (Lehrer et al., 2018). It should be noted that all of these studies have evaluated the long-term effects of HRV-BF on asthma in a stable clinic condition. Our findings, for the first time, suggested that HRV-BF, for even a single short duration episode, can improve lung function and prevent stress-induced PEF alteration in asthma.

One of the limitations of this study was that we only induced stress by Stroop test and did not apply other types of psychological stress stimuli. Therefore, the presented results may be limited to the specific stress stimulus used in this experiment. Moreover, we measured the stress level of subjects using a visual analogue scale which is a self-assessment scale and a subjective method. It is better to use quantity methods for evaluating stress in future studies. Also, due to the lack of impulse oscillometry, we could not continuously assess the short-term alteration of respiratory resistance during stress. Moreover, this study did not allow us to consider possible interactions between anti-asthma medications and HRV indices, which may contribute to RSA and autonomic reactivity during rest and stress. Finally, the participants were demographically restricted to women and young individuals. Future investigations are needed to be performed on females as well as males in multiple centers with more subjects to increase the validity of the study.

In conclusion, HRV-BF may be a promising protective complementary approach in order to reduce lung function impairment and asthma exacerbation due to psychological stress. However, the acute and chronic effects of HRV-BF on asthma and its susceptibility to stress-induced airway constriction require further investigation.

Funding

This study was supported by grants from Tarbiat Modares University to Niloofar Taghizadeh.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resp.2019.01.011.

References

Bali, A., Jaggi, A.S., 2015. Clinical experimental stress studies: methods and assessment. Rev. Neurosci. 26 (5), 555–579. https://doi.org/10.1515/revneuro-2015-0004.

Canning, B.J., Fischer, A., 2001. Neural regulation of airway smooth muscle tone. Respir. Physiol. https://doi.org/10.1016/S0034-5687(00)00208-5.

Censi, F., Calcagnini, G., Cerutti, S., 2002. Coupling patterns between spontaneous rhythms and respiration in cardiovascular variability signals. Comput. Methods Programs Biomed. 68, 37–47. https://doi.org/10.1016/S0169-2607(01)00158-4.

Delaney, J.P., Brodie, D.A., 2000. Effects of short-term psychological stress on the time and frequency domains of heart-rate variability. Percept. Mot. Skills 91 (2), 515–524. https://doi.org/10.2466/pms.2000.91.2.515.

Ernst, G., 2017. Heart-Rate Variability-More than Heart Beats? Front. Public Health 11 (5), 240.

Garcia-Araújo, A.S., Pires Di Lorenzo, V.A., Labadessa, I.G., Jürgensen, S.P., Di Thommazo-Luporini, L., Garbim, C.L., Borghi-Silva, A., 2015. Increased sympathetic modulation and decreased response of the heart rate variability in controlled asthma. J. Asthma 52 (3), 246–253. https://doi.org/10.3109/02770903.2014.957765.

Garrard, C.S., Seidler, A., McKibben, A., McAlpine, L.E., Gordon, D., 1992. Spectral analysis of heart rate variability in bronchial asthma. Clin. Auton. Res. 2 (2), 105–111. https://doi.org/10.1007/BF01819665.

Gayrard, P., Orehek, J., Grimaud, C., Charpin, J., 1979. Mechanisms of the broncho-constrictor effects of deep inspiration in asthmatic patients. Thorax 34 (2), 234–240. https://doi.org/10.1136/thx.34.2.234.

Gift, A.G., 1989. Visual analogue scales: measurement of subjective phenomena. Nurs. Res. 38 (5), 286–288.

Global Initiative For Asthma (GINA), 2017. Global Strategy For Asthma Management and Prevention. Global Initiative for Asthma. https://doi.org/10.1183/09031936.00138707. http://ginasthma.org/2017-gina-report-global-strat.

Goldstein, D.S., Bentho, O., Park, M.Y., Sharabi, Y., 2011. Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp. Physiol. 96 (12), 1255–1261.

Isenberg, S.A., Lehrer, P.M., Hochron, S., 1992. The effects of suggestion and emotional arousal on pulmonary function in asthma: a review and a hypothesis regarding vagal mediation. Psychosom. Med. https://doi.org/10.1097/00006842-199203000-00006.

Janssens, T., Steele, A.M., Rosenfield, D., Ritz, T., 2017. Airway reactivity in response to repeated emotional film clip presentation in asthma. Biol. Psychol. 123, 1–7. https://doi.org/10.1016/j.biopsycho.2016.11.006.

Koyanagi, K., Koya, T., Sasagawa, M., Hasegawa, T., Suzuki, E., Arakawa, M., Gejyo, F., 2009. An analysis of factors that exacerbate asthma, based on a japanese questionnaire. Allergol. Int. 58 (4), 519–527. https://doi.org/10.2332/allergolint.09-OA-0095.

Kullowatz, A., Rosenfield, D., Dahme, B., Magnussen, H., Kanniess, F., Ritz, T., 2008. Stress effects on lung function in asthma are mediated by changes in airway inflammation. Psychosom. Med. 70 (4), 468–475. https://doi.org/10.1097/PSY.0b013e31816f9c2f.

Lavoie, K.L., Cartier, A., Labrecque, M., Bacon, S.L., Lemière, C., Malo, J.L., et al., 2005. Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? Respir. Med. 99 (10), 1249–1257. https://doi.org/10.1016/j.rmed.2005.03.003.

Lehrer, P.M., Carr, R.E., Smetankine, A., Vaschillo, E., Peper, E., Porges, S., et al., 1997. Respiratory sinus arrhythmia versus neck/trapezius EMG and incentive inspirometry biofeedback for asthma: a pilot study. Appl. Psychophysiol. Biofeedback 22 (2), 95–109. https://doi.org/10.1023/A:1026224211993.

Lehrer, P.M., Vaschillo, E., Vaschillo, B., 2000a. Resonant frequency biofeedback training to increase cardiac variability: rationale and manual for training. Appl. Psychophysiol. Biofeedback 25 (3), 177–191. https://doi.org/10.1023/A:1009554825745.

Lehrer, P., Smetankin, A., Potapova, T., 2000b. Respiratory sinus arrhythmia biofeedback therapy for asthma: A report of 20 unmedicated pediatric cases using the Smetankin method. Appl. Psychophysiol. Biofeedback 25 (3), 193–199. https://doi.org/10.1023/A:1009506909815.

Lehrer, P., Feldman, J., Giardino, N., Song, H.S., Schmaling, K., 2002. Psychological aspects of asthma. J. Consult. Clin. Psychol. 70 (3), 691–711. https://doi.org/10.1037//0022-006X.70.3.691.

Lehrer, P.M., Vaschillo, E., Vaschillo, B., Lu, S.E., Eckberg, D.L., Edelberg, R., et al., 2003. Heart rate variability biofeedback increases baroreflex gain and peak expiratory flow. Psychosom. Med. 65 (5), 796–805. https://doi.org/10.1097/01.PSY.0000089200.81962.19.

Lehrer, P.M., Vaschillo, E., Vaschillo, B., Lu, S.-E., Scardella, A., Siddique, M., Habib, R.H., 2004. Biofeedback treatment for asthma. Chest 126 (2), 352–361. https://doi.org/10.1378/chest.126.2.352.

Lehrer, P., Vaschillo, E., Lu, S.E., Eckberg, D., Vaschillo, B., Scardella, A., Habib, R., 2006. Heart rate variability biofeedback: Effects of age on heart rate variability, baroreflex gain, and asthma. Chest 129 (2), 278–284. https://doi.org/10.1378/chest.129.2.278.

Lehrer, P., Vaschillo, B., Zucker, T., Graves, J., Katsamanis, M., Aviles, M., Wamboldt, F., 2013. Protocol for heart rate variability biofeedback training. Biofeedback 41 (3), 98–109. https://doi.org/10.5298/1081-5937-41.3.08.

Lehrer, P.M., Irvin, C.G., Lu, S.E., Scardella, A., Roehmheld-Hamm, B., Aviles-Velez, M., et al., 2018. Heart rate variability biofeedback does not substitute for asthma steroid controller medication. Appl. Psychophysiol. Biofeedback 43 (1), 57–73. https://doi.org/10.1007/s10484-017-9382-0.

Lewis, M.J., Short, A.L., Lewis, K.E., 2006. Autonomic nervous system control of the cardiovascular and respiratory systems in asthma. Respir. Med. https://doi.org/10.1016/j.rmed.2006.01.019.

Lutfi, M.F., 2015. Patterns of heart rate variability and cardiac autonomic modulations in controlled and uncontrolled asthmatic patients. BMC Pulm. Med. 15 (1). https://doi.org/10.1186/s12890-015-0118-8.

Malik, M., Bigger, J., Camm, A., Kleiger, R., 1996. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur. Heart J. 17, 354–381 https://doi.org/0195-668X/96/030354 + 28.

Martínez-Moragón, E., Perpiñá, M., Belloch, A., De Diego, A., Martínez-Francés, M., 2003. Determinants of dyspnea in patients with different grades of stable asthma. J. Asthma 40 (4), 375–382. https://doi.org/10.1081/JAS-120018637.

Mikosch, P., Hadrawa, T., Laubreiter, K., Brandl, J., Pilz, J., Stettner, H., Grimm, G., 2010. Effectiveness of respiratory-sinus-arrhythmia biofeedback on state-anxiety in patients undergoing coronary angiography. J. Adv. Nurs. 66 (5), 1101–1110. https://doi.org/

10.1111/j.1365-2648.2010.05277.x.
Miller, B.D., Wood, B.L., Lim, J.H., Ballow, M., Hsu, C.Y., 2009. Depressed children with asthma evidence increased airway resistance: “Vagal bias” as a mechanism? J. Allergy Clin. Immunol. 124 (1). https://doi.org/10.1016/j.jaci.2009.04.038.
National Asthma Education and Prevention Program, 2007. Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institutehttps://doi.org/10.1016/j.jaci.2007.09.029.
Prinsloo, G.E., Rauch, H.G.L., Karpul, D., Derman, W.E., 2013. The effect of a single session of short duration heart rate variability biofeedback on EEG: a pilot study. Appl. Psychophysiol. Biofeedback 38 (1), 45–56. https://doi.org/10.1007/s10484-012-9207-0.
Qaseem, A., Wilt, T.J., Weinberger, S.E., et al., 2011. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann. Intern. Med. 155–179.
Raoufy, M.R., Hajizadeh, S., Gharibzadeh, S., Mani, A.R., Eftekhari, P., Masjedi, M.R., 2013. Nonlinear model for estimating respiratory volume based on thoracoabdominal breathing movements. Respirology 18 (1), 108–116. https://doi.org/10.1111/j.1440-1843.2012.02251.x.
Raoufy, M.R., Ghafari, T., Darooei, R., Nazari, M., Mahdaviani, S.A., Eslaminejad, A.R., ... Hajizadeh, S., 2016. Classification of asthma based on nonlinear analysis of breathing pattern. PLoS One 11 (1). https://doi.org/10.1371/journal.pone.0147976.
Raoufy, M.R., Ghafari, T., Mani, A.R., 2017. Complexity analysis of respiratory dynamics. Am. J. Respir. Crit. Care Med. https://doi.org/10.1164/rccm.201701-0026LE.
Rennard, S., Thomashow, B., Crapo, J., et al., 2013. Introducing the COPD foundation guide for diagnosis and management of COPD, recommendations of the COPD foundation. COPD 10–378.
Richman, J.S., Moorman, J.R., 2000. Physiological time-series analysis using approximate entropy and sample entropy. Am. J. Physiol. Heart Circ. Physiol. 278 (6), H2039–H2049. https://doi.org/10.1103/physreva.29.975.
Rietveld, S., van Beest, I., 2007. Rollercoaster asthma: When positive emotional stress interferes with dyspnea perception. Behav. Res. Ther. 45 (5), 977–987. https://doi.org/10.1016/j.brat.2006.07.009.
Ritz, T., Steptoe, A., DeWilde, S., Costa, M., 2000. Emotions and stress increase respiratory resistance in asthma. Psychosom. Med. 62 (3), 401–412. https://doi.org/10.1097/00006842-200005000-00014.
Ritz, T., Kullowatz, A., Goldman, M.D., Smith, H.-J., Kanniess, F., Dahme, B., Magnussen, H., 2010. Airway response to emotional stimuli in asthma: the role of the cholinergic pathway. J. Appl. Physiol. 108 (6), 1542–1549. https://doi.org/10.1152/japplphysiol.00818.2009.
Ritz, T., Rosenfield, D., Wilhelm, F.H., Roth, W.T., 2012. Airway constriction in asthma during sustained emotional stimulation with films. Biol. Psychol. 91 (1), 8–16. https://doi.org/10.1016/j.biopsycho.2012.03.014.
Shirazi, A.H., Raoufy, M.R., Ebadi, H., De Rui, M., Schiff, S., Mazloom, R., et al., 2013. Quantifying Memory in Complex Physiological Time-Series. PLoS One 8 (9). https://doi.org/10.1371/journal.pone.0072854.
Sneed, N.V., Olson, M., Bubolz, B., Finch, N., 2001. Influences of a relaxation intervention on perceived stress and power spectral analysis of heart rate variability. Prog. Cardiovasc. Nurs. 16 (2), 57–64 79.
Souza, V.F., Costa, I.P., Silva, A.B., Lacerda, D.H., Costa, D., Oliveira, C.S., et al., 2010. Study of heart rate autonomic modulation in patients with asthma disease. Clin. Exp. Med. Lett. 51 (2), 105–108.
Stroop, J.R., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol. 18 (6), 643–662. https://doi.org/10.1037/h0054651.
Ten Brinke, A., Ouwerkerk, M.E., Zwinderman, A.H., Spinhoven, P., Bel, E.H., 2001. Psychopathology in patients with severe asthma is associated with increased health care utilization. Am. J. Respir. Crit. Care Med. 163 (5), 1093–1096. https://doi.org/10.1164/ajrccm.163.5.2004020.
Vaschillo, E., Lehrer, P., Rishe, N., Konstantinov, M., 2002. Heart rate variability biofeedback as a method for assessing baroreflex function: A preliminary study of resonance in the cardiovascular system. Appl. Psychophysiol. Biofeedback 27 (1), 1–27. https://doi.org/10.1023/A:1014587304314.
Vaschillo, E.G., Vaschillo, B., Lehrer, P.M., 2006. Characteristics of resonance in heart rate variability stimulated by biofeedback. Appl. Psychophysiol. Biofeedback 31 (2), 129–142. https://doi.org/10.1007/s10484-006-9009-3.
WHO Expert Consultation, 2004. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363 (9403), 157–163.